UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/393,803	09/10/99	LIU	M 19188PCA

EXAMINER	
LEFFERS JR, G	
ART UNIT	**PAPER NUMBER**
1636	8

000216
MERCK AND CO INC
P O BOX 2000
RAHWAY NJ 07065-0907

HM12/0117

DATE MAILED: 01/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/393,803	Liu, et al.
Examiner	**Group Art Unit**
Gerald G. Leffers Jr.	1636

X Responsive to communication(s) filed on *Oct 27, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-44* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Acknowledgment is made of applicants' amendment, filed 10/27/00, in which applicants submitted "red-lined corrections to the drawings, amended the Brief Description of the Figures, amended the continuing data, amended claim 23 and submitted replacement pages bearing a clean copy of the pending claims. Claims 1-44 are pending in this application.

Any objection or rejection made in previous Office Actions and not addressed in this Action have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 26-34, 36-38 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the art, state of the prior art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Each of the claims is directed to a gene therapy approach for generating an immune response against HIV in the cells of a vertebrate animal. The nucleic acids of the invention comprise up to several cistrons per nucleic acid construct which cistrons are either under the control of individual promoter/regulatory elements or feature two or more cistrons operatively linked to a first promoter/regulatory element (e.g. via an IRES sequence located between different cistrons such that a single transcript produces multiple polypeptides upon translation in the cell). The invention thus encompasses the complex expression of multiple coding sequences from a single nucleic construct in eukaryotic cells. Moreover, the invention encompasses the use of coordinated expression of gene products and interaction between expressed genes products and the nucleic acid construct itself to affect the ultimate expression of the desired antigenic polypeptide in vivo (e.g. expression of rev from the same construct comprising a rev-dependent gene). Finally, the invention encompasses the additional expression of immuno-stimulatory gene products from the same construct in order to enhance the level and type of immune response against the desired polypeptide. Thus, the claimed invention is exceedingly complex on multiple levels from transgene expression in eukaryotic cells to coordinate expression of gene products to stimulation of the immune response of a vertebrate organism via the expression of "foreign" genes in vivo.

Scope of the rejected claims: Given the broadest reasonable interpretation of the rejected claims upon reading the specification, the claims read upon the vaccination of a vertebrate animal, including human, against HIV. Thus, the breadth of the rejected claims, encompassing a vaccine against a pathogen for which no effective vaccine is known even now, only exacerbates the extreme complexity of the claimed invention.

Guidance from the specification: The specification provides many permutations of different nucleic acid constructs bearing multiple cistrons which can be tried in an effort to develop a sage and effective HIV vaccine. Guidance is given for different types of constructs wherein the cistrons are each transcribed under the control of separate regulatory elements or wherein the different cistrons on a given construct are transcribed as part of a single, polycistronic message. Different combinations of immunostimulatory and antigenic coding sequences are described which might be tried in order to develop an effective immune response against a pathogenic organism from which the antigen coding sequence is derived. There is no significant guidance, however, with regard to making the construction and use of such an anti-HIV vaccine in humans more predictable than had already been demonstrated in the art at the time applicants' invention was made.

The existence of working examples: Although applicants test various polynucleotide constructions in mice and primates, these systems are not acknowledged models that would reflect the human condition (e.g. see Haynes below). The specification provides examples wherein nucleic acid constructs of the invention were used to generate an anti-gp120 response in

mice, anti-gp160 response in primates (i.e. rhesus monkeys and African Green monkeys) and anti-SIV response in primates. The anti-gp120 response in mice demonstrated that the polycistronic vectors described as part of the instant invention are more effective that the equivalent combination of monocistronic in generating a specific immune response against gp120. However, as noted above, none of the model systems described by applicants is accepted in the art as being predictive of success for developing such an anti-HIV vaccine or protective response in humans. Moreover, applicants own examples demonstrate that the generation of a sustained, specific immune response in lower primates is not necessarily predictable with the nucleic acid constructs of the instant invention. In the case of an anti-SIV response, applicants' constructs generated a specific CTL response against SIV gag which subsided with time. No such specific CTL response was obtained for equivalent constructs expressing SIV nef (Example 4).

State of the art: The art of vaccinating vertebrate organisms against viral infections, at the time of applicants' invention, was well developed. However, the unique challenges presented by the HIV virus, due to its nature of attacking the helper T cell subset, present heretofore insurmountable challenges. "The difficult scientific issues before us underlie the fact that, as yet, there is no preventive HIV vaccine on the near horizon with clear prospects for clinical use." (Haynes, page 1279, column 1). "Although more is known about HIV than almost any other infectious agent, scientific questions remain unanswered that are critical to development of an HIV preventative vaccine." (Haynes, page 1279, column 3). Further, there are no animal models

for human infection. "Because of a lack of an animal model of human AIDS and because of a cohort of individuals naturally resistant to HIV infection is not available, the immune correlates of protection against HIV are not known." (page 1280, column 1). Thus, the state of the art with regard to an immune response by humans against HIV, remains underdeveloped and extensive experimentation of a discovery nature is ongoing.

Predictability of the art: The art of vaccinating a vertebrate host organism against HIV viral infection or viral epitopes is unpredictable. At the time of applicants invention, there was no model organism that exhibited an immune response to HIV that was correlative with that of humans. It is also known in the art that the surface antigens of the virus mutate rapidly, thus evading immune responses and that no protective immunity has been raised against HIV, even to date. Thus, the art of vaccinating a vertebrate against HIV infection is unpredictable.

Amount of experimentation necessary: Given the extreme complexity of the invention, featuring the use of nucleic acids directly injected into the tissue of an organism which must coordinately express multiple genes in vivo and which must generate an immune response against at least one of the gene products; given the fact that the breadth of the claims encompasses a vaccine against a pathogen for which no such effective vaccine has been developed; given the lack of significant guidance in the specification in how to make and use such nucleic acid constructs to generate such an in vivo immune response against HIV; given the lack of relevant working examples, the fact that applicants own examples with primates are not predictable and are not predictive of success in humans; given the state of the art at the time of

the invention wherein no such vaccine against HIV was known nor was thought to be available any time in the near future; and given the resulting unpredictability of the which arises from the fact that no such vaccine has been developed even to date, the fact that HIV attacks the very cell population responsible for specific anti-viral response and the nature of the highly mutable nature of the HIV virion, one of skill in the art would not be able to construct and use the claimed invention without undue, unpredictable experimentation. Thus, applicants' invention of polycistronic nucleic acid constructs and methods for inducing a protective immune response against HIV in vertebrate animals, including humans, is not considered enabled by the instant specification.

Response to Arguments

In response to a similar rejection of claims 26-34, 36-38 and 43 for lack of enablement made in the Office Action mailed 4/24/00, applicants' response mailed 10/27/00 argues essentially the following points: 1) examiner's rejection is nothing more than an "old style" 101 utility rejection, 2) the specification provides numerous examples and guides the prospective investigator through construction of several different polycistronic vectors and their use in vertebrate model systems, 3) no further experimentation is required, only "trials" in the targeted host organism, which are fully within the grasp of the skilled artisan, 4) the rejection suggests that nothing short of FDA approval subsequent to human clinical trials would be necessary to provide and enabling specification, 5) the Haynes reference bears on utility and not on enablement.

With regard to the assertion that the rejection made in the previous Office Action is nothing more than an "old style" utility rejection and the further assertion that the examiner is requiring FDA approval or human clinical trials, these assertions are inaccurate. The rejection of the claims in the previous Office Action, as in this Action, was made based upon a reasoned Wands analysis of the instant specification and the prior art. The Haynes reference was relied upon to demonstrate the state of the art at the time of the invention as well as the unpredictability of the art. In no way did the examiner address issues of utility. Nor did the examiner ever suggest or imply in any way that efficacy in human trials was required for the claimed invention to be enabled. The examiner utilized, as in the instant Action, a full-blown and careful Wands analysis of the specification and prior art to determine that it would take undue, unpredictable experimentation to make and use the claimed invention. Based upon this Wands analysis the examiner determined that the underdevelopment of the art and unpredictability of the art regarding HIV vaccination, particularly with regard to vaccination of humans, was not offset or overcome by the guidance and working examples provided in the specification.

The assertion that no more experimentation, only trials in the host organism, is necessary in order to develop and practice the claimed invention is inaccurate. Such trials themselves constitute additional experimentation. It appears applicants' response is arguing that such trials would be routine experimentation. First, such trials, even if routine and predictable, require an enormous amount of work and investment in materials and test subjects. Moreover, the outcome of such trials, based upon a careful and full Wands analysis of the prior art and specification,

would be unpredictable. Thus, the work required to make and practice the claimed invention would be undue and unpredictable experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the limitation "..a transcriptional terminator following each of the first, second or third cistron." are unclear. The phrase is unclear in that it specifies a transcriptional terminator after each of the cistrons comprised within the polynucleotide of the invention while the body of the claim specifies that each of the cistrons following the first cistron can be under the transcriptional control of a promoter controlling expression of cistrons farther upstream. It is unclear how such constructs would work if there are transcriptional termination signals separating each of the cistrons.

Claim 18 is vague and indefinite in that the phrase "A polynucleotide which comprises contiguous nucleic acid sequences which cannot replicate in eukaryotic cells.." appears to specify that the contiguous nucleic acid sequences cannot replicate in eukaryotic cells. It appears from reading the specification that the phrase is meant to specify that the entire polynucleotide cannot

replicate in eukaryotic cells. It would be remedial to amend the claim language to something like "A polynucleotide which cannot replicate in eukaryotic cells and which comprises contiguous nucleic acid sequences which are capable of being expressed..".

Claim 22 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the gene" in the claim. Does the term refer to the first gene encoding an HIV epitope or to a subsequent gene? It would be remedial to amend the claim language to clearly indicated which properties are assigned to the first gene and which are assigned to any subsequent gene sequences.

Claim 23 is vague and indefinite in that the metes and bounds of the phrase "junction sequence" as used for the different recited constructs are unclear. Many of the recited constructs appear to specify two different sequences. Are each of the different sequences part of a single junction or does each belong to a separate junction? Also, the specified constructs each have a particular name and are described in the specification as to the nature of the junctions comprised within the nucleic acid construct. In such a case, it is only necessary to refer to the nucleic acid construct by its specific name. It would be remedial to amend the claim language to simply refer to each specific construct by the name under which it is described in the specification.

Claim 24 is vague and indefinite in that it specifies a group of different HIV genes (gag, gag-protease and env) for the first gene of the construct. However, the claim does not use proper Markush language to specify the different genes. It would be remedial to amend the claim to

something like "..a gene encoding a gene product selected from the group consisting of HIV gag, HIV gag-protease and HIV env, the gene being..".

Similarly, claim 35 specifies a group of different genes as part of another nucleic acid construct of the invention. It would be remedial to amend the claim to include proper Markush language as well. For example, the claim could be amended to something like "the immunomodulatory or immunostimulatory genes being selected from the group consisting of genes encoding GM-CSF, IL-12 and B7 protein.

Claim 36 is vague and indefinite in that metes and bounds of the phrase "..comprising sequences encoding an antigenic HIV epitope, optionally, HIV REV, and sequences encoding a B7 protein.." are unclear. Which of the 3 specified sequences is optional? The first sequence, a combination of the second and third sequences or just the second sequence? It would be remedial to amend the claim language to clearly indicate which sequences are intended to be optional for the nucleic acid recited in the method of claim 36.

Claims 39 and 41 are vague and indefinite in that the claims use grammatically incorrect terms such as "an eukaryotic" or "an heterologous". It would be remedial to amend the claim language to "a eukaryotic" and "a heterologous". Also, the metes and bounds of step (d) of claim 41 are unclear. Does the open reading frame specified in step (d) constitute a different, second open reading frame from that specified in part (b)? Upon reading the specification it appears that part (d) of claim 41 is meant to specify a second HIV gene open reading frame in addition to the

first one specified in part (a). It would be remedial to amend the claim language to more clearly indicated that a second HIV open reading frame is specified for the polynucleotide of claim 41.

Claim 42 is vague and indefinite in that the metes and bounds of the phrase "..comprising multiple expression constructs each of which is capable of inducing expression in mammalian tissue of more than a single cistron encoding antigens.." are unclear. As the claim is written, it is unclear as to whether constructs which induced expression of viral antigens from an integrated, dormant virus within the target cell genome would be encompassed by the instant claim. Upon reading the specification, it appears instead that the limitation is intended to specify that each construct comprises and expresses multiple cistrons encoding antigens obtained from pathogens or tumors. It would be remedial to amend the claim language to clearly indicate where the cistrons encoding relevant antigens are located.

Claim 43 needs to be broken up more clearly into separate alternative embodiments of the claimed nucleic acid. It appears, upon reading the specification and the claim, that the claim intends to specify two different embodiment of a polycistronic nucleic acid construct wherein the two cistrons of the construct can be either independently regulated or regulated as part of a single polycistronic message. However, as the claim is written, this dichotomy is not clear. It would be remedial to amend the claim language such that the choice between two different embodiments of a particular type of polycistronic nucleic acid is clear.

Claim 44 is vague and indefinite in that the claim specifies particular elements present in a nucleic acid construct in a figure. This is improper and inherently indefinite in that every

particular limitation embodied within figure may not be readily apparent to the skilled artisan and is open to interpretation by different artisans. It is required that the particular limitations to be met by a particular construct be incorporated directly into the claim language.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Richard Schwartz, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GGL

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER

January 16, 2001